Medicine®

Diagnostic Accuracy Study

OPEN

Monitoring Hepatocyte Dysfunction and Biliary Complication After Liver Transplantation Using Quantitative Hepatobiliary Scintigraphy

Si-Juan Zou, MD, Dong Chen, MD, PhD, Yan-Zhao Li, PhD, Dun-Feng Du, MD, PhD, Zhi-Shui Chen, MD, PhD, and Xiao-Hua Zhu, MD, PhD

Abstract: The significance of hepatobiliary scintigraphy (HBS) for hepatic graft function assessment was established mostly on retrospective studies and was not widely recognized due to the lack of quantitative data and variation in accuracy. This prospective study was performed to investigate the effectiveness of quantitative HBS for assessing hepatocyte dysfunction and biliary complication in liver transplant recipients.

In 57 recipients who had undergone orthotopic liver transplantation, a total of 67 dynamic ^{99m}Tc-EHIDA scans were performed and quantitative parameters including the hepatocyte extraction fraction (HEF), time to maximum hepatic radioactivity (T_{max}), and time for peak activity to decrease by 50% ($T_{1/2}$) were calculated. The scintigraphic results based on the 3 parameters were compared against the final diagnosis. A ROC curve analysis was carried out to identify the cutoff value of T_{max} for diagnosis of biliary stricture. Correlation between the parameters of postoperative HBS and conventional biochemical liver function indices were also analyzed.

Quantitative ^{99m}Tc-EHIDA HBS had an overall sensitivity of 94.12% (16/17), specificity of 93.33% (42/45), and diagnostic accuracy of 93.55% (58/62) for detecting hepatocyte dysfunction and biliary complication in liver transplant recipients. The recommended cutoff value of T_{max} for diagnosis of post-transplant biliary stricture was set at 15.75 min with a sensitivity of 100.0% and a specificity of 94.0%. The scintigraphic parameters (HEF, T_{max}) were statistically significantly associated with the conventional liver function parameters.

Quantitative ^{99m}Tc-EHIDA HBS offers a noninvasive imaging modality with high sensitivity and specificity to diagnose hepatocyte dysfunction as well as distinguish between patients with or without biliary stricture following liver transplantation. Furthermore, HEF and T_{max} values obtained from dynamic HBS show good correlation with conventional liver function parameters.

(*Medicine* 94(45):e2009)

Abbreviations: γ-GGT = gamma-glutamyl transferase, ALB = albumin, ALP = alkaline phosphates, ALT = alanine aminotransferase, AST = aspartate aminotransferase, DBIL = direct bilirubin, EHIDA = diethyl-iminodiacetic acid, HBS = hepatobiliary scintigraphy, HCC = hepatocellular carcinoma, HEF = hepatic extraction fraction, LT = liver transplantations, OLT = orthotopic liver transplantation, ROI = region of interest, TBIL = total bilirubin.

INTRODUCTION

Currently >6000 liver transplantations (LT) are performed per year in the United States and nearly half as many in Mainland China.[1,2] Liver transplantation has now a generally accepted and effective treatment option for fulminant liver failure, primary liver tumors and virtually all types of end-stage liver disease with 1- and 5-year overall survival rate of 82% and 71%, respectively.[3–4] Better management of liver transplant recipients after transplantation is crucial for outcomes and will likely help graft salvage in certain cases. During the post-transplant period, and more generally, the critical period of the first year, close follow-up is required for monitoring the graft function and revealing any post-transplant complications which may lead to graft failure.

To define therapeutic strategies for transplant dysfunction patients, it is of great importance to determine the functional performance of the graft liver and biliary tract. Hepatobiliary scintigraphy (HBS) has been used as an important noninvasive imaging modality for evaluating liver function (both total and regional) and postsurgical biliary complications. Previous studies have described the utility of HBS for visual assessment of graft function and detection of biliary complications in liver transplant recipients. However, nonquantitative visual interpretation by HBS is weak in terms of evidence-based approach, and this method is also highly physician dependent. The sensitivity of visual analysis of HBS to assess post-transplant complications is reported with a wide range between 63% and 93%, and even lower at 56.2% in a recent study.[5–7] Quantitative analysis of HBS is promising for more accurate estimation of liver function and postsurgical complications. Several studies evaluated the clinical use of quantitative HBS parameters such as the hepatic uptake rate (HUR), which mainly measures blood-pool-corrected hepatic uptake, and hepatic extraction fraction (HEF) that estimates the degree of hepatocellular dysfunction.[8,9] In a small-scale study of 10 pediatric liver

Editor: Jin Chul Paeng.
Received: August 27, 2015; revised: October 3, 2015; accepted: October 10, 2015.
From the Department of Nuclear Medicine (SJZ, YZL, XHZ); and Institute of Organ Transplantation, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China (DC, DFD, ZSC).
Correspondence: Xiao-Hua Zhu, Department of Nuclear Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Ave, Wuhan, China (e-mail: evazhu@vip.sina.com). Zhi-Shui Chen, Institute of Organ Transplantation, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Ave, Wuhan, China (e-mail: evazhu@vip.sina.com, zschen@tjh.tjmu.edu.cn).
Funding: this work was supported by National Science Foundation of China (NSFC) (No. 81271600), the Natural Science Founds of Hubei Province in China (No. 2011CDB551), the Independent Innovation Founds of Huazhong University of Science and Technology (No. 2011JC060) and the Clinical Foundation of Tongji Hospital (No.2010026).
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000002009

transplant recipients, researchers observed that 6 recipients with abnormal scintigraphic parameters (HEF, T_{max}, and $T_{1/2}$) had positive biopsy findings, including acute rejection in 1 case and hepatocyte damage/cholestasis in the other 5.[10] Although the quantitative evaluation of HBS seems to be more helpful for identifying transplant dysfunction, the efficiency of quantitative HBS that measures HEF, T_{max}, and $T_{1/2}$ values for the diagnosis of hepatocyte dysfunction and biliary complications in liver transplant recipients are not quite clear. Moreover, there have been limited studies reporting the correlation between the data of quantitative HBS and laboratory biochemical parameters in post-transplant patients.

This prospective study was designed to assess the performance of quantitative HBS scans for monitoring graft dysfunction and biliary complication in patients who had undergone orthotopic liver transplantation (OLT). The correlations between data of scintigraphic and biochemical parameters after transplantation were also evaluated. Long-term objective of this study is to eventually facilitate quantitative HBS as a simple and efficient method for post-transplant evaluation and be accepted in routine clinical practice.

PATIENTS AND METHODS

Patients

This study was approved by the independent ethics committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. All patients for liver transplantation have completed the China Organ Transplant Response System registration process. From January 2011 to January 2014, a total of 57 recipients without cardiac or kidney dysfunction, who had undergone OLT in our hospital, were recruited with written informed consent. Among the 57 patients, 56 received full-size OLT and 1 received split-liver (right) OLT. The mean age of these patients was 45.82 ± 10.88 years; 47 were men and 10 were women. The indications for LT were cirrhosis 30 (52.63%) including hepatitis B in 20 patients, hepatitis C in 3, autoimmune hepatitis in 4, primary biliary cirrhosis in 1, schistosomiasis in 2, and primary liver tumors 27 mainly related to hepatocellular carcinoma (HCC) (45.62%). The patient characteristics and transplant information are summarized in Table 1.

TABLE 1. Patient Characteristics

Variable	Mean ± SD (%)
Male:female (n)	47: 10
Age (y)	45.82 ± 10.88
Indication for LT (n)	
Cirrhosis	30 (52.63%)
Hepatitis B	20
Hepatitis C	3
Autoimmune	4
Primary biliary cirrhosis	1
Schistosomiasis	2
Hepatocellular carcinoma	26 (45.62%)
Hilar cholangiocarcinoma	1 (1.75%)
Type of transplantation (n)	
Full size OLT	56 (91.07%)
Split OLT (right)	1 (1.79%)
Biliary anastomosis (n)	
Duct-to-duct	57 (100%)
Mean interval between LT and HBS (day)	30

LT = liver transplantations, HBS = hepatobiliary scintigraphy, OLT = orthotopic liver transplantation, SD = standard deviation.

METHODS

Serology Tests

Blood liver function tests were performed to measure biochemical parameters 1-day pre-HBS scan. Values of post-transplant aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin (ALB), total bilirubin (TBIL), direct bilirubin (DBIL), alkaline phosphates (ALP), and gamma-glutamyl transferase (γ-GGT) were included. The relationships between data of quantitative HBS and the postoperative biochemical parameters were then analyzed.

Hepatobiliary Scintigraphy (HBS)

Hepatobiliary scans were performed on all recipients during the postoperative period (median interval time 30 days). Sequential anterior images were acquired directly after intravenous injection of 370 MBq Tc-99m-diethyl-iminodiacetic acid (EHIDA) using a low energy, high-resolution dual-head collimator (Infinia Hawkeye, GE Healthcare Technologies). The field of view included the heart, the liver, and the upper abdomen. Data were acquired at a rate of 1 frame per 60 s over 60 min using a 128×128 matrix. Then delayed static images for 5 min in a 256×256 matrix were acquired at 1 h, 2 h, and if needed at 4 h and 24 h after injection.

All images were analyzed by a nuclear medicine physician who was unaware of the patients' clinical scenarios and presentations. Three HBS parameters including hepatocyte extraction fraction (HEF), the time to maximum hepatic radioactivity (T_{max}) and the time required for peak activity to decrease by 50% ($T_{1/2}$) were used for quantitative evaluation of the HBS images. First, a region of interest (ROI) was drawn over the left ventricle of the heart (~50 pixels) excluding the aorta and scatter from the liver. A second ROI was drawn over the right lobe of the liver (~50–80 pixels) with minimal inclusion of biliary activity. Time–activity curves were generated and then HEF values were calculated using a deconvolution method previously described.[11] Second, a hepatic-ROI (~10–15 pixels) was drawn over the right upper lobe of graft live from which the time–activity curve was generated; the T_{max} and $T_{1/2}$ values can be obtained from the curve. Finally, the scintigraphic imaging patterns were classified into 4 groups as follows.[10–11]

Normal: normal extraction of radiotracer (HEF>90%) and excretion into the biliary tract and bowel ($5\,min \leq T_{max} \leq 15\,min$ and $T_{1/2} < 60\,min$).

Graft dysfunction: markedly low extraction and excretion of radiotracer (HEF<50% and $T_{max} < 15\,min$).

Biliary stricture: delayed excretion of radiotracer into the biliary tract and bowel ($T_{max} > 15\,min$ and $T_{1/2} > 60\,min$).

Bile leakage: unusual radiotracer collection outside the hepatobiliary passage, which increases with time.

Reference Standards

The final diagnosis of graft rejection was confirmed by liver biopsy within 1 week after HBS scan. The determination of biliary complications was on the basis of percutaneous transhepatic cholangiography (PTC), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), and/or liver biopsy. Patients were considered normal when clinical assessment and radiological follow-up >1 month after the HBS were uneventful.

Statistical Analysis

Quantitative HBS parameters between groups according to the final diagnosis were compared by analysis of variance (ANOVA) and multiple comparison tests. Receiver operating characteristic curve (ROC) analysis was performed to identify the cutoff value of T_{max} for diagnosis of post-transplant biliary stricture. Correlation between data of quantitative HBS and the postoperative biochemical parameters in recipients were tested using the Pearson and Spearman correlation coefficient.

RESULTS

Five cases were excluded because of imaging artifacts induced by patients' motion during the dynamic scan. Thus, a total of 62 HBS scans carried out on 52 patients after OLT were finally included for analysis. Postoperative biochemical parameters and data of quantitative HBS are shown in Table 2. Of the 62 HBS scans, 19 (30.65%) of the studies in 16 patients were abnormal including 3 scans of hepatocyte dysfunction, 15 of biliary stricture, and 1 of bile leakage. The clinical evaluation and quantitative HBS diagnosis of the 62 scans in 52 patients are summarized in Table 3. Graft rejection was diagnosed in 4 patients (76.92%) by liver biopsy. Additionally, biliary strictures in 12 patients (19.23%, 12 scans) and biliary leakage in 1 patient (1.92%) were confirmed by MRCP and PTC, respectively.

In the 43 normal studies without graft liver dysfunction and biliary complications, 42 (93.33%) of the scans had true negative HBS finding. There was 1 instance of false-negative HBS with normal HEF and T_{max} values; the result of liver pathology in this case showed mild acute rejection. All 3 scans of hepatocyte dysfunction were true positives with graft rejection confirmed by liver biopsy. The detection of biliary stricture in 12 patients was a true positive finding in 12/15 studies and a false positive in 3 scans. In 2/3 of the false positive HBS cases, there was evidence of biliary strictures by MRCP during the second HBS scan. Follow-up of these 12 patients showed recovery in 11 following endoscopic therapy, the remaining 1 patient undergone re-transplantation because of graft failure.

The biopsy, radiological diagnosis (PTC, ERCP, MRCP), or clinical follow-up were taken as reference standards to calculate the sensitivity, specificity, and accuracy of quantitative HBS for evaluating hepatocyte dysfunction and biliary complication in patients who had undergone OLT. The overall sensitivity of quantitative ^{99m}Tc-EHIDA HBS for detection of post-transplant biliary stricture was 100% (12/12), and the specificity was 94% (47/50). Quantitative HBS had an overall sensitivity of 94.12% (16/17), specificity of 93.33% (42/45), and diagnostic accuracy of 93.55% (58/62) for assessing hepatocyte dysfunction and biliary complication in liver transplant recipients.

The HEF value of HBS was markedly lower in patients with graft rejection (Table 4). However, there was a wide range of HEF, 9.75–95.96% and 44.65–100%, in patients with rejection and biliary stricture, respectively (Figure 1A). The T_{max} values in patients with biliary strictures were significantly prolonged and could be discriminatory from the normal patients and patients with rejection ($P < 0.001$) (Figure 1B). The recommended cutoff value of T_{max} for diagnosis of post-transplant biliary stricture was set at 15.75 min with a sensitivity of 100.0%, and a specificity of 94.0% (Figure 2). When T_{max} value was set at 23.0 min, the sensitivity was 66.7%, and the specificity was 100%.

Pearson and Spearman Correlation revealed that the HEF value positively correlated with the postoperative albumin ($r = 0.269$; n = 62), whereas, it negatively correlated with the ALT ($r = 0.262$; n = 62), AST ($r = 0.264$; n = 62), total bilirubin ($r = 0.877$; n = 62), and direct bilirubin ($r = 0.874$; n = 62). T_{max} value was negatively correlated with the albumin

TABLE 2. Postoperative Biochemical Parameters and Data of Quantitative HBS

Variable	Mean ± SD	Range
ALB (g/L)	37.32 ± 5.45	(28.00–47.50)
ALT (U/L)	67.84 ± 105.91	(4.00–633.00)
AST (U/L)	47.07 ± 57.64	(6.00–374.00)
TBIL (μmol/L)	35.88 ± 69.50	(5.20–377.80)
DBIL (μmol/L)	27.39 ± 56.73	(2.60–302.40)
γ-GGT (U/L)	202.29 ± 237.75	(22.00–1269.00)
ALP (U/L)	189.61 ± 154.88	(44.00–814.00)
T_{max} (min)	14.02 ± 6.91	(0.50–38.50)
$T_{1/2}$ (min)	NA	(0.50–NR)
HEF (%)	89.12 ± 20.47	(3.53–100.00)

γ-GGT = gamma-glutamyl transferase, ALB = albumin, ALP = alkaline phosphates, ALT = alanine aminotransferase, AST = aspartate aminotransferase, DBIL = direct bilirubin, HEF = hepatic extraction fraction, NA = not available, NR = not reach (> 60 min), SD = standard deviation, TBIL = total bilirubin.

TABLE 3. Clinical Evaluation and Quantitative HBS Diagnosis of 62 Scans

	Quantitative HBS Diagnosis			
Final Diagnosis (N = 62)	Hepatocyte Dysfunction	Biliary Stricture	Bile Leak	Normal
Normal (n = 45)		3		42
Bile leak (n = 1)			1	
Biliary stricture (n = 12)		12		
Rejection (n = 4)	3			1

HBS = hepatobiliary scintigraphy.

TABLE 4. HBS Parameters in Groups According to Reference Standard: Scan-Based Analysis (1 Bile Leakage not Included)

Variable (N = 61)	Normal (n = 45)	Biliary Stricture (n = 12)	Rejection (n = 4)
T_{max} (min)	11.69 ± 2.74	25.50 ± 6.38*	7.08 ± 7.46*
$T_{1/2}$ (min)	39.34 ± 7.97	NA	NA
HEF (%)	97.25 ± 3.83	83.12 ± 15.59*	40.66 ± 43.03*

HEF = hepatic extraction fraction, NA = not available.
* $P < 0.01$.

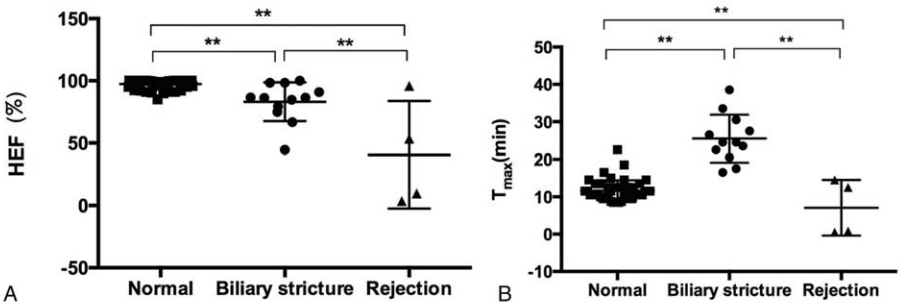

FIGURE 1. Distributions of HEF (A) and T_{max} (B) on HBS for the normal, biliary stricture, and rejection patients. Statistical significance of difference was assessed by analysis of variance and posthoc least significant difference tests. ($^{**}P<0.001$). HBS = hepatobiliary scintigraphy, HEF = hepatocyte extraction fraction.

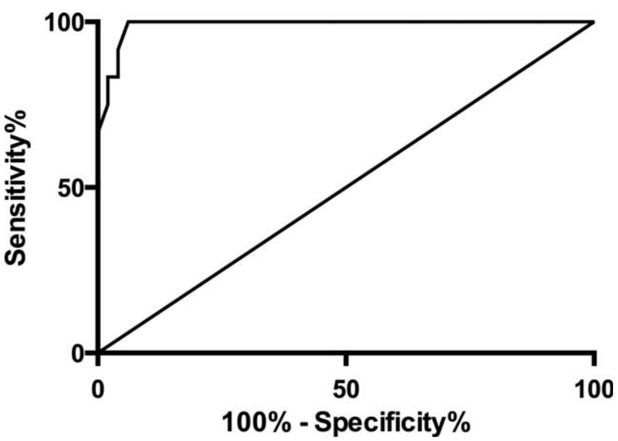

FIGURE 2. ROC curve analysis of T_{max} for diagnosis of biliary stricture post LT. The cutoff value was set at 15.75 min with a sensitivity of 100.0%, and a specificity of 94.0%. (Area under the curve = 0.9898; 95% confidence interval 0.9718–1.008). LT = liliver transplantations, ROC = receiver operating characteristic curve.

($r = 0.259$; n = 62), total bilirubin ($r = 0.272$; n = 62), and direct bilirubin ($r = 0.261$; n = 62). There was a positive correlation between the T_{max} and alkaline phosphatase ($r = 0.275$; n = 62) (Table 5).

DISSCUSSION

Although improved survival rates have been achieved due to better organ selection and advances in surgical techniques, each LT recipient may experience a few challenges that might lead to graft failure during the post-transplant period.[12] Hepatocyte dysfunction due to graft rejection and biliary complications is the frequent cause of post-transplant morbidity and mortality. Therefore, close postoperative follow-up using various monitoring modalities for early diagnosis of transplant dysfunction are of high importance with respect to patient outcome.

Hepatobiliary scintigraphy has been used as an important noninvasive imaging modality for determining the functional performance of graft liver and the biliary tract.[13] Previous studies focused primarily on the visual information of HBS imaging for assessment of graft function and post-transplant biliary complications in recipients, resulting in an unsatisfied sensitivity as low as 56.2%.[7] Although various quantitative HBS techniques, such as curve-based[14] deconvolution analysis[15] or in combination with tracer kinetic modeling[16] have been subsequently introduced for better assessment of hepatic function, the effectiveness of quantitative HBS for monitoring hepatocyte dysfunction and post-transplant biliary complications is not quite clear. In this study, we determined HEF, T_{max}, and $T_{1/2}$ for quantitative evaluation of dynamic HBS after LT. The scintigraphic diagnosis of hepatocyte dysfunction and biliary stricture was based on these 3 parameters. Our results show that the quantitative HBS is of high accuracy (93.55%) detecting graft dysfunction and biliary complications after OLT. This suggests that quantification of HEF, T_{max}, and $T_{1/2}$ values from dynamic HBS can be a more reliable method for monitoring the functional status of the graft liver and biliary tract.

Biliary stricture was the most common postoperative complication that occurred in 12 patients (23.08%) in our study. From the perspective of clinical practice, biliary complications were once considered the technical ''Achilles heel'' of OLT and still occur in 10% to 30% following whole-organ OLT.[17] Since late biliary complications several months to years after grafting are usually caused by recurrence of early post-transplant

TABLE 5. Correlation Between the Parameters of HBS and Postoperative Biochemical Parameters: Scan-Based Analysis

Variable	ALB	ALT	AST	TBIL	DBIL	γ-GGT	ALP
HEF	0.269(0.036)*	−0.262(0.041)*	−0.264(0.040)*	−0.877(0.000)*	−0.874(0.000)*	−0.116(0.454)	−0.108(0.516)
T_{max}	−0.259(0.044)*	0.069(0.595)	0.120(0.354)	−0.272(0.032)*	−0.261(0.041)*	0.195(0.129)	0.275(0.031)*
$T_{1/2}$	NA	NA	NA	NA	NA	NA	NA

ALB = albumin, ALP = alkaline phosphates, ALT = alanine aminotransferase, AST = aspartate aminotransferase, DBIL = direct bilirubin, γ-GGT = gamma-glutamyl transferase, HEF = hepatic extraction fraction, NA = not available, TBIL = total bilirubin.
$^{*}P<0.05$.

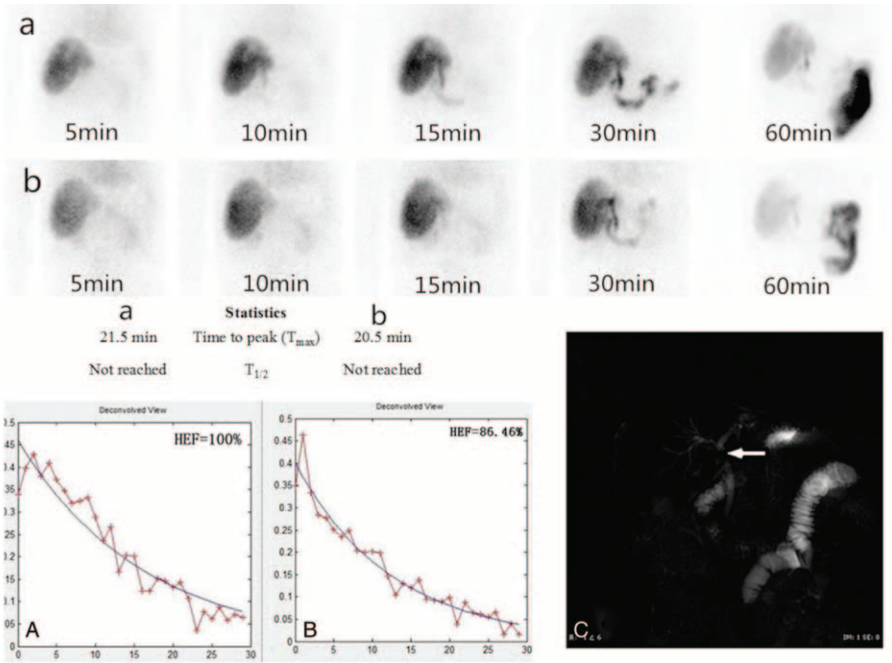

FIGURE 3. A 52-year-old man with biliary stricture at the anastomosis confirmed by MRCP (c, arrow) following orthotopic liver transplantation (OLT). Quantitative ^{99m}Tc-EHIDA scintigraphy at 1 month (A) and 5 month (B) after transplantation revealed abnormally prolonged T_{max} (a: 21.5 min; b: 20.5 min) of the graft liver, which indicated that the patient might have suffered from biliary stricture. The HEF value on the first scan was normal (a: 100%), However, 4 months later, reduced HEF (b: 86.46%) was seen on the follow-up scan. HEF = hepatic extraction fraction, MRCP = magnetic resonance cholangiopancreatography, OLT = orthotopic liver transplantation.

complications or those failed to completely resolve, an accurate and timely diagnosis of biliary complications post LT is important in guiding appropriate surgical or medical therapy.[18] In our study, the sensitivity and specificity of HBS for diagnosis of post-transplant biliary stricture were 100% and 94%, respectively. This suggests that quantitative HBS is a very helpful test for detecting biliary stricture. Moreover, according to the results of the present study, the group of patients with biliary stricture had significantly prolonged T_{max} values in comparison with the normal recipients and patients with graft rejection ($P < 0.01$). These results were of considerable interest, because the T_{max} value of HBS could seemingly distinguish patients with or without biliary stricture after LT. Thus, we performed an ROC curve analysis for the 2 categories. The recommended cutoff value of T_{max} for diagnosis of post-transplant biliary stricture was set at 15.75 min with a sensitivity of 100.0%, and a specificity of 94.0%. In the 15 studies with biliary stricture, 12 were true positives. On the other hand, in 2/3 of the false positive HBS with no clinical symptoms, there was evidence of biliary strictures by MRCP following the second HBS scan. This suggests that findings of the 2 studies revealed initial phase of biliary stricture.

Although there is no accurate method to determine the functional significance of bile strictures after liver transplantation and although endoscopic therapy is the first-line treatment in patients with extra-hepatic bile duct strictures, there is no quantitative method to monitor the treatment response. The quantification of HEF, T_{max}, and $T_{1/2}$ values was a decision-support methodology for the complex clinical decisions, although $T_{1/2}$ values went beyond 60 min and could not be reached in a subset of patients. The HEF value focuses on the degrees of hepatocyte dysfunction and/or cholestasis.[9] Both groups with rejection and biliary stricture showed impairment of HEF presumably reflecting hepatocellular dysfunction at the time of the study.

Another remarkable finding in the present study was that 3 of 12 patients, who had biliary stricture on HBS scans, had a normal HEF on the first scan. By contrast, with prolonged biliary strictures, concomitant hepatocellular dysfunction occurred, and reduced HEF could be seen on the follow-up scan (Figure 3). Finally, among the 12 patients with biliary stricture, 11 with mild hepatocellular damage (HEF>65%) showed recovery following endoscopic therapy, whereas the remaining 1 patient with significant liver damage (HEF = 44.65%) received a second liver transplant as a salvage therapy. Therefore, such quantitative information about the degree of biliary stricture is essential and has a great impact on surgical decision-making in post–transplantation period.

Biliary leaks may arise from the anastomosis, the cystic duct, or T-tube.[19] Because clinical signs and symptoms of bile leaks are nonspecific in immune-suppressed recipients and delay in the recognition of bile leaks is associated with high morbidity and mortality rates, imaging is crucial for establishing an early diagnosis and determining appropriate treatment. In the post-LT patient, a fluid collection demonstrated by anatomic imaging studies is often a nonspecific finding. Hepatobiliary scintigraphy as a functional imaging modality plays an important role in not only definitive confirmation that such fluid is of biliary origin, but also in localizing active leakage and evaluating the rate of leakage.[20] In our study, biliary leakage comprised only 1.92% of the complications. The extremely low proportion of biliary leakage reflects its low incidence as a post-LT complication in our institute. Based on amount and rate of tracer observed outside the anastomosis, we classified the bile leaks as small. Then, following internal biliary drainage, the patient showed smooth recovery.

Rejection is the immunological attack by the host on the graft, and the mechanisms of rejection of liver transplants may differ in degrees and cellular and/or humoral involvement.[21] The typical pathological features of liver allograft rejection include portal inflammation, bile duct inflammation, and venous inflammation. The differential diagnosis of rejection from post-transplant biliary complications is often challenging as early symptoms of both conditions are nonspecific and can cause a cholestatic pattern of liver enzyme elevation. A few studies have addressed the fact that the distinction between rejection and biliary complications was difficult by means of HBS, because certain patients with rejection and hyperbilirubinemia showed results of total biliary obstruction on vision-based HBS scintigraphy.[6] However, a more recent published study by Lee et al suggested that PPI values derived from dynamic HBS could help discern rejection and distinguish rejection from biliary obstruction or recurrent hepatitis.[22] Another study by Krishnamurthy et al indicated that the quantitative analysis of HBS method may possess practical value in separating severe hepatocyte disease from biliary tract disease.[23] Our research focused on the quantitative parameters of HEF, T_{max}, and $T_{1/2}$ for evaluation of the liver graft function. As is shown in Table 3, graft rejection was confirmed in patients with hepatocyte dysfunction in all 3 studies. One case with acute cellular rejection and 1 with acute humoral rejection showed significantly reduced HEF and T_{max} value on HBS imaging. Besides, the third patient, who showed moderate reduced HEF and T_{max} value was confirmed mild chronic rejection. This suggests that HEF combined with T_{max} and $T_{1/2}$ value have certain value for identifying graft rejection and differentiating it from biliary complications. Notably there was 1 instance of false-negative HBS with normal data on HBS. The patient had no clinical symptoms or signs of graft dysfunction; however, the result of liver pathology showed mild acute rejection. In some centers, protocol biopsies were suggested for detection of the so-called subclinical acute rejection. However, protocol biopsy does not often make cost-effective assessments of subclinical acute rejection because the number of such patients is small. According to our experience, as histological findings are overlapped or even inconclusive for certain patients with graft rejection, it is important to review prior biopsies combined with laboratory, radiological, and clinical findings. Although there is no ''reference standard'', in our opinion, reduced values of HEF and T_{max} derived from dynamic HBS can be a useful diagnostic indicator of graft dysfunction caused by rejection.

Our study demonstrated a good correlation between the data of scintigraphic and biochemical parameters after transplantation. Only albumin positively correlated with postoperative HEF. ALT, AST, total bilirubin, and direct bilirubin were negatively correlated with postoperative HEF. Kansoul et al have shown similar results indicating that high HEF is correlated with long-term patient survival.[24] Performing the blood liver function test and HBS scan on liver transplant recipients at a reasonable time outside the recommended time windows of ischemia reperfusion damage (~1–2 weeks) gave our study greater advantage compared with other reports that focused on the peritransplant period. Moreover, there was a negatively correlation between T_{max} and albumin, total bilirubin, and direct bilirubin. These findings strongly support HEF, T_{max}, and $T_{1/2}$ as a metric of hepatobiliary function and as a valuable indicator of transplant dysfunction caused by rejection and biliary stricture.

The main goal of this prospective study was to assess the performance of quantitative HBS scan for monitoring hepatocyte dysfunction and biliary complication in patients who had undergone OLT. The results revealed a high diagnostic accuracy (93.55%) of quantitative ^{99m}Tc-EHIDA HBS for detecting graft dysfunction and biliary complication in liver transplant recipients. The reliability of diagnosing graft dysfunction and biliary stricture was improved by using quantitative analysis of scintigraphic data. This suggests that values of HEF and T_{max}, indexes of hepatic uptake and excretion, can be valuable diagnostic indicators of transplant dysfunction caused by graft rejection and biliary complication. More importantly, the T_{max} value of HBS was able to distinguish between patients with and without biliary stricture after OLT. As such, a recommended cutoff value of T_{max} for diagnosis of post-transplant biliary stricture was set at 15.75 min with a sensitivity of 100.0%, and a specificity of 94.0%. At the same time, we identified a good correlation between scintigraphic and conventional liver function parameters after transplantation suggesting that the HEF and T_{max} derived from HBS imaging are valuable indices for assessing the functional performance of the graft and biliary tract.

The present study also has a couple of limitations. First, the small number of patients with positive findings warrants further studies with a larger number of cases. Secondly, the hepatic ^{99m}Tc-EHIDA uptake can be influenced by hyperbilirubinemia to some extent in a few cases. It is therefore important to tailor the study to individual patients taking account of the clinical scenarios and presentations.

CONCLUSION

Quantitative ^{99m}Tc-EHIDA HBS offers a noninvasive imaging modality with high sensitivity and specificity to diagnose hepatocyte dysfunction as well as distinguish between patients with or without biliary stricture following liver transplantation. Furthermore, HEF and T_{max} values obtained from dynamic HBS show good correlation with conventional liver function parameters.

REFERENCES

1. Wang H, Jiang W, Zhou Z, et al. Liver transplantation in Mainland China: the overview of CLTR 2011 annual scientific report. *Hepatobiliary Surg Nutr.* 2013;2:188–197.
2. What is a liver transplant. In: Liver transplant. American Liver Foundation. 2015. http://www.liverfoundation.org/abouttheliver/info/transplant/.
3. Adam R, Karam V, Delvart V, et al. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). *J Hepatol.* 2012;57:675–688.
4. Zarrinpar A, Busuttil RW. Liver transplantation: past, present and future. *Nat Rev Gastroenterol Hepatol.* 2013;10:434–440.
5. Anselmi M, Lancberg S, Deakin M, et al. Assessment of the biliary tract after liver transplantation: T tube cholangiography or IODIDA scanning. *Br J Surg.* 1990;77:1233–1237.
6. Kim JS, Moon DH, Lee SG, et al. The usefulness of hepatobiliary scintigraphy in the diagnosis of complications after adult-to-adult living donor liver transplantation. *Eur J Nucl Med Mol Imaging.* 2002;29:473–479.
7. Kim YJ, Lee KT, Jo YC, et al. Hepatobiliary scintigraphy for detecting biliary strictures after living donor liver transplantation. *World J Gastroenterol.* 2011;17:2626–2631.

8. Ekman M, Fjalling M, Holmberg S, Person H. IODIDA clearance rate: a method for measuring hepatocyte uptake function. *Transplantation Proceedings.* Feb 1992; 24(1):387–388.
9. Howman-Giles R, Moase A, Gaskin K, et al. Hepatobiliary scintigraphy in a pediatric population: determination of hepatic extraction fraction by deconvolution analysis. *J Nucl Med.* 1993;34:214–221.
10. Gencoglu E, Karakayali H, Moray G. Evaluation of pediatric liver transplant recipients using quantitative hepatobiliary scintigraphy. *Transplant Proc*. 2002; 34(6):2160-2162.
11. Brown PH, Juni JE, Lieberman DA, et al. Hepatocyte versus biliary disease: a distinction by deconvolutional analysis of technetium-99m IDA time-activity curves. *J Nucl Med.* 1988;29:623–630.
12. Alqahtani SA. Update in liver transplantation. *Discov Med.* 2012;14:133–141.
13. Lambie H, Cook AM, Scarsbrook AF, et al. Tc99m-hepatobiliary iminodiacetic acid (HIDA) scintigraphy in clinical practice. *Clin Radiol.* 2011;66:1094–1105.
14. Leonard JC, Hitch DC, Manion CV. The use of diethyl-IDA Tc 99m clearance curves in the differentiation of biliary atresia from other forms of neonatal jaundice. *Radiology.* 1982;142:773–776.
15. Tagge EP, Campbell DA Jr, Reichle R, et al. Quantitative scintigraphy with deconvolutional analysis for the dynamic measurement of hepatic function. *J Surg Res.* 1987;42:605–612.
16. Gambhir SS, Hawkins RA, Huang SC, et al. Tracer kinetic modeling approaches for the quantification of hepatic function with technetium-99m DISIDA and scintigraphy. *J Nucl Med.* 1989;30:1507–1518.
17. Safdar K, Atiq M, Stewart C, et al. Biliary tract complications after liver transplantation. *Expert Rev Gastroenterol Hepatol.* 2009;3:183–195.
18. Kirimlioglu V, Tatli F, Ince V, et al. Biliary complications in 106 consecutive duct-to-duct biliary reconstruction in right-lobe living donor liver transplantation performed in 1 year in a single center: a new surgical technique. *Transplant Proc.* 2011; 43(3):917-920.
19. Londono MC, Balderramo D, Cardenas A. Management of biliary complications after orthotopic liver transplantation: the role of endoscopy. *World J Gastroenterol.* 2008;14:493–497.
20. Ziessman HA. Acute cholecystitis, biliary obstruction, and biliary leakage. *Semin Nucl Med.* 2003;33:279–296.
21. Neil DA, Hubscher SG. Current views on rejection pathology in liver transplantation. *Transplant Int.* 2010;23:971–983.
22. Lee JY, Hu W, Lee KH, et al. Differentiation of liver transplantation complications by quantitative analysis of dynamic hepatobiliary scintigraphy. *Nucl Med Commun.* 2012;33:255–261.
23. Doo E, Krishnamurthy GT, Eklem MJ, et al. Quantification of hepatobiliary function as an integral part of imaging with technetium-99m-mebrofenin in health and disease. *J Nucl Med.* 1991;32:48–57.
24. Kansoul HA, Axelsson R, Yamamoto S, et al. Parameters obtained by hepatobiliary scintigraphy have significant correlation with biochemical factors early after liver transplantation. *Acta Radiol.* 2007;48:597–604.